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## *The Dilemma of Defining Diabetes Mellitus in the Aging Population*

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*A total of 1,009 persons were given a 100-gram glucose solution orally after a three-day regimen of a diet preparation and an overnight fast. Fasting and two-hour plasma glucose levels were determined for each subject and the results tabulated. Most of the persons tested were in the sixth, seventh or eighth decade of life with 43 persons between 80 and 89 years of age. The frequency of fasting plasma glucose determinations above 140 mg per dl varied from 3 percent to 7 percent between the sixth and ninth decades. Those persons with two-hour plasma glucose values above 200 mg per dl represented 8 percent of the 50 to 59 year old group and the percentages rose respectively to 12 percent, 16 percent and 21 percent in the 60 to 69, 70 to 79 and 80 to 89 year old groups. Finally, those who had fasting plasma glucose levels below 140 mg per dl and two-hour glucose values between 140 and 200 mg per dl were tabulated according to decade of life. This group varied from 9 percent to 15 percent between ages 20 and 59 and represented 20 percent to 22 percent of those in the seventh, eighth and ninth decades. In light of the known deterioration of glucose tolerance with aging, some stratification of blood glucose concentrations should be applied with age, but to what degree and what diagnostic criteria should be applied are still unclear.*

RAPIDLY EXPANDING KNOWLEDGE concerning the pathogenesis of diabetes mellitus has led to an increased awareness of the need to revise the nomenclature, diagnostic criteria and classification of diabetes. The recognition of a lack of uniformity in defining diabetes mellitus and other categories of glucose intolerance led to the estab-

lishment of a workshop for creating an international classification system. The results and recommendations of the workshop have been published by the National Diabetes Data Group of National Institutes of Health.<sup>1</sup> The aims of the workshop were to establish a classification of diabetes that would serve as a framework for the collection of epidemiologic data on the etiology, natural history and impact of diabetes and its complications in diverse populations. The workshop further sought to "aid the clinician in cate-

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## ABBREVIATION USED IN TEXT

OGTT=oral glucose tolerance test

gorizing and managing patients who have various degrees of glucose intolerance or who possess characteristics which place them at increased risk of developing diabetes."<sup>11(p1040)</sup>

One requirement of the terminology and classification system was to be able to place an individual at any time throughout life in only one class (although that person may subsequently require reclassification) so that each class would contain a population as homogeneous as possible. Further, the system was to use only simple clinical measurements or descriptive observations that are readily obtainable and have biologic significance.

Recognizing that the diagnosis of diabetes mellitus in an aging population has become increasingly more meaningful in recent decades, we have focused our attention on this aspect. Although it is well accepted that glucose tolerance deteriorates with age, the precise criteria to be applied at each decade of life and the relationship between these criteria and the sequelae of diabetes mellitus in the aging population remain unresolved.<sup>2-12</sup>

The specific criteria for establishing the diagnosis of diabetes mellitus, according to the National Diabetes Data Group, require that a 75-gram glucose load be given and that the fasting plasma glucose level must be above 140 mg per dl on two separate tests or that the two-hour post-glucose-load value exceed 200 mg per dl on two separate tests with one other measurement before the two-hour point being over 200 mg per dl on two separate tests as well. In the present study, a 100-gram oral glucose load was administered and a single venous plasma glucose level determined in the fasting state and two hours following the glucose load. Therefore the methods applied in the present study and practiced for the past five years are not strictly comparable with the criteria established by the National Diabetes Data Group for the diagnosis of diabetes mellitus. Nevertheless, we considered it worthwhile to apply the criteria of elevated fasting plasma glucose values above 140 mg per dl and two-hour post-glucose-load values greater than 200 mg per dl to the population studied to establish the frequency of glucose abnormalities by decades in a population skewed toward older age groups.

TABLE 1.—*Profile of Subjects Tested, With Distribution by Sex and Decade of Life*

	<i>Number in Category</i>	<i>Ages</i>	<i>Men</i>	<i>Women</i>
	62 ...	20-29	17	45
	70 ...	30-39	21	49
	71 ...	40-49	23	48
	154 ...	50-59	52	102
	377 ...	60-69	146	231
	232 ...	70-79	96	136
	43 ...	80-89	23	20
TOTAL	1,009 ...		378	631

### Methods and Subjects

The data presented are the results of studies conducted during semiannual "Diabetes Detection Drives" held at the Eisenhower Medical Center, Rancho Mirage, California. All subjects were screened to exclude people known to have diabetes. A diet consisting of 150 to 300 grams of carbohydrate was provided for three days before the test. On the morning of the test, after an overnight fast, a venous blood specimen was collected for glucose level determination. Immediately thereafter a 100-gram oral glucose solution was given and ingested within ten minutes. Exactly two hours later, a second specimen of venous blood was collected. All blood specimens were put into fluoridated vacutainers to limit glycolysis during the interim between sampling and analysis and all specimens were analyzed within eight hours of collection. All glucose level determinations were carried out on plasma by a Beckman System 1 using the glucose oxidase method.

### Results

Table 1 shows the total number of patients studied, grouped according to sex and decade of life. Of note is the predominant age distribution in the sixth, seventh and eighth decades with a representative sampling of octogenarians as well. This demographic distribution represents the age distribution of the retirement community in which the hospital is located and, though unique nationally, may be characteristic of the age distribution of other retirement communities.

Table 2 shows by decade the frequency of fasting plasma glucose determinations above 140 mg per dl. Of interest is the abrupt increase beyond the 50th year, which stabilizes between 2 percent and 4 percent up to the eighth decade.

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TABLE 2.—Subjects With Fasting Plasma Glucose (FPG) Levels Over 140 mg per dl, With Distribution by Sex and Decade of Life

Ages	Number in Category	FPG > 140 mg/dl Number	Percentage	Men Number	Women Number
20-29 ..	62	..	..	..	..
30-39 ..	70	..	..	..	..
40-49 ..	71	..	..	..	..
50-59 ..	154	3	2	1	2
60-69 ..	377	15	4	11	4
70-79 ..	232	5	2	2	3
80-89 ..	43	3	7	..	3
TOTAL .	1,009	26	3	14	12

TABLE 3.—Two-Hour Plasma Glucose (PG) Levels Above 200 mg per dl Following 100-Gram Oral Glucose Load, With Distribution by Sex and Decade of Life

Ages	Number in Category	2 hr Postprandial PG > 200 mg/dl Number	Percentage	Men Number	Women Number
20-29 ..	62	..	..	..	..
30-39 ..	70	..	..	..	..
40-49 ..	71	..	..	..	..
50-59 ..	154	12	8	6	6
60-69 ..	377	47	12	24	23
70-79 ..	232	37	16	10	27
80-89 ..	43	9	21	2	7
TOTAL .	1,009	105	10	42	63

TABLE 4.—Subjects With Fasting Plasma Glucose (FPG) Level Under 140 mg per dl and Two-Hour Plasma Glucose Over 200 mg per dl, Distribution by Decade of Life

Ages	Number	FPG < 140 mg/dl 2 hr PP > 200 mg/dl Number	Percentage
20-29 .....	62	..	..
30-39 .....	70	..	..
40-49 .....	71	..	..
50-59 .....	154	10	6.5
60-69 .....	377	31	8.2
70-79 .....	232	33	14.2
80-89 .....	43	6	14.0
TOTAL .....	1,009	80	7.9

TABLE 5.—Subjects With Fasting Plasma Glucose (FPG) Levels Below 140 mg per dl and Two-Hour Plasma Glucose Levels Between 140 and 200 mg per dl, With Distribution by Sex and Decade of Life

Ages	Number in Category	FPG < 140 mg/dl 2 hr > 140 mg/dl but < 200 mg/dl Number	Percentage	Men Number	Women Number
20-29 ..	62	9	15	3	6
30-39 ..	70	6	9	2	4
40-49 ..	71	9	13	3	6
50-59 ..	154	22	14	4	18
60-69 ..	377	77	20	31	46
70-79 ..	232	52	22	26	26
80-89 ..	43	9	21	5	4
TOTAL .	1,009	184	18	74	110

The seeming increase in frequency in the 80 to 89 years age group must be interpreted with caution in view of the small number of subjects found to be abnormal in that age group. Chi-square analysis of all patients younger than 60 (357 patients) as compared with those over 60 years (652 patients) showed a statistically increased frequency of fasting plasma glucose levels above 140 mg per dl ( $P < .01$ ) in the group older than 60 years.

Table 3 shows the surprisingly high frequency of elevated two-hour serum glucose determinations of 200 mg per dl and above occurring in an ascending manner in the 60 to 69, 70 to 79 and 80 to 89 year old age groups.

Table 4 lists those subjects by decade who had fasting plasma glucose values below 140 mg per dl and two-hour plasma glucose levels above 200 mg per dl. There was an increasing frequency of this divergence in each decade over age 50. Chi-square analysis of all patients under 60 years old (227 patients) as compared with those over 60 years (652 patients) showed a statistically increased frequency of patients with fasting plasma glucose values below 140 mg per dl and two-hour plasma glucose values above 200 mg per dl in those subjects 60 years of age and older ( $P < .005$ ).

Table 5 presents those subjects with fasting plasma glucose levels below 140 mg per dl and a two-hour plasma glucose concentration between 140 and 200 mg per dl. At each decade, the results were found to equal or exceed the frequency of abnormal values found with observation of either fasting glucose or two-hour glucose levels over 200 mg per dl (Table 3).

## Discussion

Almost 60 years after Hagedorn's initial efforts at defining normality of glucose tolerance, there still exists no unanimity of opinion concerning the interpretation of glucose tolerance tests in aging people.<sup>3</sup> One reason for this lack of agreement is the fact that there is no clear division between diabetic and nondiabetic populations in either fasting or two-hour oral glucose tolerance test (OGTT) blood glucose levels. Rather, the frequency distribution in a representative population shows a continuous unimodal distribution from low to high, skewed to the higher level.<sup>13</sup> Consequently, no features of the curve allow patients with diabetes to be distinguished from those without diabetes. This is in contrast to the Pima

Indian population and the Western Samoan-Polynesian population, where one finds a bimodal distribution between the nondiabetic and diabetic populations—that is, two-hour plasma glucose level below 200 mg per dl defining the nondiabetic population and falling in the first mode, whereas diabetic patients with two-hour levels above 200 mg per dl fall in the second mode.<sup>14-16</sup> Moreover, the observation that diabetic sequelae of retinopathy and nephropathy are confined to those subjects with two-hour plasma glucose levels above 200 mg per dl gives clinical credence to this natural subdivision of the diabetic from the nondiabetic Pima Indian and Western Samoan-Polynesian populations. As an extension of these observations, there has been a tendency by some to arbitrarily define all subjects in the general population with two-hour plasma glucose values above 200 mg per dl as having diabetes mellitus.

Compounding the problem of a necessarily arbitrary selection of numbers with which one is to define the diabetic population is the fact that, in general, glucose tolerance seems to decrease with age. Although a number of possibilities have been proposed to explain the mechanism or mechanisms for this phenomenon, the critical question exists as to whether the decline in performance that occurs with aging should be considered a general adaptive process affecting most of the population—in which case standards for normality should be further age adjusted—or whether the decline in tolerance is caused by the progressive selective evolution of increasing numbers of people with true diabetes—in which case age adjustment would be inappropriate.<sup>13</sup>

In support of the former position is the realization that failure to readjust postglucose values with age would result in the diagnosis of diabetes mellitus in up to 75 percent of certain populations tested, leading in fact to general condemnation of the glucose tolerance test by some investigators.<sup>17</sup> The alternative point of view, that the increasing number of abnormal glucose values with age represents a selection of the true diabetic population, is supported by the observation that some diabetic sequelae, particularly cardiovascular disease and retinopathy, are seen more commonly in aging hyperglycemic patients as compared with aging normoglycemic people.<sup>14,18,19</sup>

Some stratification of glucose measurements should be applied with age but the question exists as to what criteria should be applied and to what

degree. In a critical review of this subject, O'Sullivan<sup>8</sup> takes the position that the role of diagnostic standards should take precedence over age effects for their contribution to the frequency of abnormal tests. In agreement with O'Sullivan, it would seem that there is no valid reason for discounting the influence of age on blood glucose standards simply because they might give rise to "unacceptably" high prevalence rates. There is general agreement that what is needed is the documentation of the health significance of the standards adopted. In other words, do the criteria established to diagnose the presence of diabetes mellitus correlate with the clinical development of vascular complications from the disease? Rushforth, Miller and Bennett<sup>20</sup> have looked at this question in the Pima Indians, a population group with a distinct bimodal distribution of fasting and two-hour plasma glucose level abnormalities. Only the hyperglycemic group showed a higher prevalence of retinopathy and nephropathy, suggesting that this group does indeed constitute those with diabetes mellitus.<sup>20-22</sup> Additionally, Jarrett and Keen<sup>23</sup> found that the risk of specific diabetic complications became important only in people with capillary whole blood glucose concentrations exceeding 200 mg per dl two hours after a 50-gram oral glucose load and those who had overnight fasting blood glucose concentrations exceeding 110 mg per dl. These observations appear to refute the suggestion by Siperstein<sup>17</sup> that it is unlikely that subtle degrees of glucose intolerance would have any deleterious effect on tissue capillaries. Consequently, abnormal fasting and two-hour postprandial plasma glucose values seen in aging people is not a benign process and does bear clinical relevance as a predictive indicator for those patients in whom vascular complications are more likely to develop.

If one attempts to apply simple criteria to the establishment of the diagnosis of diabetes mellitus in aging, then fasting plasma glucose and two-hour OGTT values seem to be pertinent. Based on the results obtained with 1,009 subjects, an elevated fasting plasma glucose level of 140 mg per dl and above occurred in approximately 5 percent of subjects from the sixth through the eighth decades, with a small and insignificant rise to 7 percent in the ninth decade. Hence, a fasting plasma glucose value above 140 mg per dl probably constitutes a valid means of diagnosing the presence of diabetes mellitus through the ninth decade of life. This is in

good agreement with the data of O'Sullivan<sup>8</sup> who found a trivial increase in fasting plasma glucose levels with age, averaging 1 to 2 mg per dl each decade.

A two-hour OGTT value above 200 mg per dl also seems to be a valid indicator of abnormality diagnostic of diabetes mellitus at any age even though, as evident in this report, there is a statistically increased frequency of elevated two-hour glucose values above 200 mg per dl beyond the age of 59. For reasons explained previously, we accept that a finding of a two-hour plasma glucose level over 200 mg per dl, regardless of age, should always be considered abnormal.<sup>8,24</sup>

Finally, it has been variously reported that after a 100-gram oral glucose load, the two-hour plasma glucose level will rise at a rate of from 6 to 13 mg per dl each decade.<sup>3,8</sup> If one accepts a value below 140 mg per dl as normal for younger populations, the criterion most commonly employed by the US Public Health Service,<sup>25</sup> Fajans and Conn,<sup>26</sup> the British Diabetic Association<sup>27</sup> and the World Health Organization,<sup>28</sup> then it seemed appropriate to determine the number of subjects encompassed in the present report with two-hour plasma glucose values between 140 and 200 mg per dl (see Table 5). Interestingly, the figure varied from 9 percent to 20 percent from the third through the sixth decade and then remained fairly constant at 20 percent to 22 percent during the seventh, eighth and ninth decades. These are subjects to whom the terms *borderline* or *chemical* diabetes would apply but that, in view of the ambiguities caused by their advancing age, we would not choose to identify as abnormal at at present. Rather, we would agree with recent comments by Davidson that "Because of the social and employment as well as the insurance ramifications of labeling a patient diabetic, the diagnosis should be avoided" in this group until the clinical significance of this borderline abnormality of glucose tolerance is resolved.<sup>4(p699)</sup>

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